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L3	L2 and oral$	68	L3
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L1	$cyclodextrin same fentanyl	2	L1

END OF SEARCH HISTORY

L3: Entry 60 of 68 File: USPT Jun 2, 1998

DOCUMENT-IDENTIFIER: US 5759573 A
** See image for Certificate of Correction **
TITLE: Cyclodextrin liposomes encapsulating pharmacologic compounds and methods for their use

Abstract Text (1):
Liposomes containing cyclodextrin in the encapsulated aqueous phase are useful for encapsulation of biologically active substances, especially those which are hydrophilic. The encapsulated cyclodextrin facilitates a slow, controlled release of pharmacologic compounds from the liposomes. The novel methods of the present invention allow the treatment of a variety of pathophysiological states by administering the cyclodextrin-containing liposomes encapsulating the pharmacologic compounds. The present invention also provides a novel method of extending the half life of a pharmacologic compound in an animal.

Brief Summary Text (7):
Liposome delivery systems have been proposed for a variety of pharmacologically active compounds including antibiotics, hormones and anti-neoplastic agents (Liposomes, 1983, Marc J. Ostro, Ed., Marcel-Dekker, Inc., New York, 1983). The use of liposomes to encapsulate pharmacologic agents and the efficacy of liposomal delivery systems differs according to the water-and lipid-solubility of the drug. For example, hydrophilic substituted for encapsulation in multivesicular liposomes. In contrast, hydrophobic, water insoluble compounds tend to be incorporated into the lipid bilayer. These compounds, therefore, are not well suited for encapsulation into the aqueous internal chambers of a liposome delivery system. The cyclodextrin class of compounds, especially .beta.-cyclodextrin, has been used successfully to solubilize water-insoluble hydrophobic compounds (Strattan, January 1992, Pharm. Tech. 68-74; Strattan, February 1992, Pharm. Tech. 52-58; Stern, DN&P, 2:410-415, 1989; Pagington, Chem. Brit. 23:455-458, 1987).

Brief Summary Text (12):
In one embodiment of the present invention, there is provided a liposome composition, comprising a water soluble compound encapsulated in said liposome, wherein said liposome composition contains encapsulated cyclodextrin.

Brief Summary Text (13):
In another embodiment of the present invention, there is provided a method of treating a pathophysiological state in an individual comprising administering a liposome composition to the individual, said composition comprising a pharmacologically effective amount of a water soluble compound encapsulated in said liposome, wherein said liposome composition contains encapsulated cyclodextrin.

Brief Summary Text (14):
In yet another embodiment of the present invention, there is provided a method of increasing the half-life of a compound in an animal comprising the step of administering an admixture of liposomes encapsulating the compound, wherein said liposome encapsulates cyclodextrin.

Brief Summary Text (19):
The term "MVL-CD-MTX" means a formulation containing methotrexate encapsulated into

multivesicular liposomes in the presence of cyclodextrin.

Drawing Description Text (3):
FIG. 1 shows the concentrations of methotrexate in cerebrospinal fluid (CSF) after intracisternal injection of 100 .mu.g (0.22 .mu.mol) of multivesicular liposomes encapsulating methotrexate and cyclodextrin (MVL-CD-MTX) (closed circle, free; open square, total) or as unencapsulated methotrexate (closed square). Each data point represents mean and standard deviation from three rats.

Drawing Description Text (10):
FIG. 8 shows the intraperitoneal concentrations of methotrexate after intraperitoneal injection of 10 mg/kg (22 .mu.moles/kg) of methotrexate as unencapsulated methotrexate (open circles), unencapsulated cyclodextrin-methotrexate complex (shaded triangles) or multivesicular liposome encapsulated methotrexate, MVL-CD-MTX (shaded circles, free; open boxes, total). Each point represents the mean and the standard deviation from a group of three mice.

Drawing Description Text (11):
FIG. 9 shows the amounts of methotrexate remaining within the peritoneal cavity after injection of 10 mg/kg (22 .mu.moles/kg) of methotrexate as unencapsulated methotrexate (open circles), unencapsulated cyclodextrin- methotrexate complex (closed triangles) or multivesicular liposome encapsulated methotrexate, MVL-CD-MTX (shaded boxes). Each point represents the mean and the standard deviation from a group of three mice.

Detailed Description Text (2):
The present invention is directed to forming inclusion complexes of water-soluble compounds, such as methotrexate, with cyclodextrins, preferably .beta.-cyclodextrin, and to encapsulating the inclusion complex into liposomes for controlled release. For use in the practice of this invention the cyclodextrin preferably forms an inclusion complex with the water soluble compound wherein the apolar cavity of the cyclodextrin is occupied by or sequesters the compound sufficiently to slow the rate of release from the liposome composition. The rim or the periphery of the inclusion complex is hydrophilic with the result that the inclusion complex forms a solution in aqueous media. The cyclodextrin-complexed water soluble substance can then be encapsulated into liposomes.

Detailed Description Text (3):
In addition to preventing incorporation of water soluble compounds into the lipid layers of the liposomes during their formation, Applicants have discovered that formation of an inclusion complex results in a reduction in the rate of release of the hydrophilic compound from the liposome compared to the rate of release of the same compound encapsulated in the absence of the cyclodextrin.

Detailed Description Text (4):
The present invention provides a liposome composition, comprising a pharmacologically active amount of a biologically active compound encapsulated in said liposome, wherein said liposome composition further contains encapsulated cyclodextrin. Preferably, the biologically active compound is water soluble. In the practice of this invention, the water soluble compound generally has water solubility of greater than about 1 .mu.g/ml, preferably greater than about 100 .mu.g/ml, and most preferably greater than about 1 mg/ml, in the absence of cyclodextrin.

Detailed Description Text (6):
Cyclodextrins are chiral, toroidal-shaped molecules formed by the action of the enzyme cyclodextrin transglycosylase on starch. These cyclic oligomers contain from 6 to 12 glucose units bonded through .alpha.-(1,4)-linkages. The three smallest homologs, .alpha.-cyclodextrin, .beta.-cyclodextrin and .gamma.-cyclodextrin are available commercially; larger homologs must be produced and isolated individually.

The secondary 2- and 3-hydroxy groups line the mouth of the cyclodextrin cavity and have a staggered orientation. The primary 6-hydroxyls are at the opposite end of the molecule. The inside of the cyclodextrin cavity is relatively hydrophobic since all hydroxyls are directed toward the outside of the molecule.

Detailed Description Text (7):
It is specifically contemplated that many different types of cyclodextrins would be useful in the compositions and methods of the present invention. For example, the present invention may use natural .alpha.-, .beta.- or .gamma. cyclodextrins. Similarly, the present invention may utilize semisynthetic substituted cyclodextrins such as; methyl cyclodextrins, ethyl cyclodextrins, hydroxyethyl cyclodextrins, hydroxypropyl cyclodextrins, branched cyclodextrins, cyclodextrin polymers or monosuccinyl dimethyl .beta.-cyclodextrin. Most preferred for the compositions and methods of the present invention is 2-hydroxypropyl-.beta.-cyclodextrin.

Detailed Description Text (8):
Generally, the concentration of cyclodextrin used in preparing the liposomes of the present invention is that which slows the release of a pharmacologic compound from the liposome after administration to an animal. Preferably, the cyclodextrin is present in the liposome composition in an amount of from about 10 milligrams per ml to about 400 milligrams per ml. More preferably, the amount of cyclodextrin in the liposome is about 100 mg/ml.

Detailed Description Text (9):
Generally, the liposome of the present invention may be any that when prepared with encapsulated cyclodextrin provides slow, controlled release of pharmacologic compounds. Preferably, the liposome is selected from the group of unilamellar, multilamellar and multivesicular liposomes. Most preferably, the liposome is a multivesicular liposome.

Detailed Description Text (10):
Generally, the biologically active compound encapsulated in the liposome oil the present invention may be any whose release rate from a liposome encapsulating cyclodextrin is slower than that in the absence of the cyclodextrin. Therapeutic biologically active compounds may be selected from the general group consisting of anti-neoplastic agents, anti-infective agents, anti-depressives, antiviral agents, anti-nociceptive agents, anxiolytics and hormones.

Detailed Description Text (17):
Representative examples of anti-nociceptives useful in the compositions and methods of the present invention include hydromorphine, oxycodone, fentanyl, morphine and meperidine.

Detailed Description Text (19):
The present invention also provides a method of increasing the half-life of a pharmacologic compound in an animal comprising the step of administering an admixture of liposomes encapsulating the pharmacologic compound, wherein said liposome further encapsulates cyclodextrin.

Detailed Description Text (20):
The present invention additionally provides a method of treating a pathophysiological state in an individual comprising administering a liposome composition to the individual, said composition comprising a therapeutically effective amount of a compound encapsulated in said liposome, wherein said liposome composition further encapsulates cyclodextrin. The term "therapeutically effective" as it pertains to the compositions of the invention means that biologically active therapeutic agent is present in the aqueous phase within the vesicles at a concentration sufficient to achieve a particular medical effect for which the therapeutic agent is intended. Examples, without limitation, of desirable medical

effects that can be attained are chemotherapy, antibiotic therapy, and regulation of metabolism. Exact dosages will vary depending upon such factors as the particular therapeutic agent and desirable medical effect, as well as patient factors such as age, sex, general condition, and the like. Those of skill in the art can readily take these factors into account and use them to establish effective therapeutic concentrations without resort to undue experimentation.

Detailed Description Text (22):
The liposomes of the present invention may be administered by any desired route. For example, administration may be intrathecal, intraperitoneal, subcutaneous, intramuscular, intravenous, intralymphatic, oral and submucosal. Administration may also be to different kinds of epithelia including the bronchiolar epithelia, the gastrointestinal epithelia, the urogenital epithelia and various mucous membranes in the body. As one skilled in the art will appreciate, the best route of administration may depend upon the biologically active compound selected. For instance, although methotrexate can be given orally, parenteral administration has certain advantages. The absorption rate of methotrexate after oral administration is highly variable among patients and appears to be saturable. In contrast, absorption of the drug after im or sc administration is much more predictable and complete, resulting in higher serum concentrations than after an oral dose.

Detailed Description Text (23):
Cyclodextrin-containing liposomes are useful in extended-release drug delivery of subcutaneously administered pharmacological agents for several reasons. They are quite stable in storage. Moreover, the drug can be released over extended time periods, both in vitro and in vivo. Their sponge-like internal structure, results in efficient encapsulation into a chambers, stability in storage, and extended release in vivo. For instance, the half-life in plasma of methotrexate can be increased by 206-fold over that of free methotrexate, and with peak plasma concentration was 126-fold lower compared to unencapsulated methotrexate. As a consequence of the significant modifications of the pharmacokinetics achieved by encapsulation of a drug encapsulated in the liposome in the presence of cyclodextrin, drug potency can be increased by over 100 fold. For instance the potency of methotrexate can be increased by 130 fold through administration in accordance with the teachings of this invention, and LD.sub.50 can be decreased 110 fold. These changes in potency and LD.sub.50 indicate no significant change in therapeutic index due to introduction into the liposomes during encapsulation of the biologically active compound.

Detailed Description Text (28):
Synthesis of Multivesicular Liposome-Methotrexate-.beta.Cyclodextrin Formulation, MVL-CD-MTX

Detailed Description Text (29):
Multivesicular liposomes encapusulating methotrexate in the presence of cyclodextrin (MVL-CD-MTX) were prepared using a method described by Kim et al (Cancer Treat. Rep. 71:705, 1987) with some modifications. Briefly, for each batch of MVL-CD-MTX, the discontinuous aqueous phase consisted of 2-hydroxypropyl-.beta.-cyclodextrin solution (100 mg/ml), HCl (0.1N) and methotrexate (10 mg/ml). One ml of the discontinuous aqueous phase was added into a one dram vial containing 13.9 .mu.mol dioleoyl lecithin, 3.15 .mu.mol dipalmitoyl phosphalidy/glycerol, 22.5 .mu.mol cholesterol, 2.7 .mu.mol triolein and 1 ml chloroform. The vial was attached horizontally to the head of a vortex mixer and shaken at maximum speed for 6 minutes. One-half of the resulting "water-in-oil" emulsion was expelled rapidly through a narrow-tip Pasteur pipette into each of two 1-dram vials, each containing 2.5 ml water, glucose (32 mg/ml) and free-base lysine (40 .mu.M). Each vial was then shaken on the vortex mixer for 5 seconds at maximum speed to form chloroform spherules. The chloroform spherrule suspensions in the two vials were transferred into a 250-ml Erlenmeyer flask containing 5 ml water, glucose (32 mg/ml), and free base lysine (40 mM). A stream of nitrogen gas at 7 liter per minute was used to

evaporate the chloroform over a 10-15 minute period a 37.degree. C. The MVL-CD-MTX particles were then isolated by centrifugation at 600.times.g for 5 minutes and washed three times with 0.9% NaCl solution.

Detailed Description Text (56):
With MVL-CD-MTX, neurotoxicity can be reduced by keeping most of the initial bolus of methotrexate within the multivesicular liposomes and yet tumor kill enhanced by maintaining the free methotrexate to just above the minimum cytotoxic concentration for an extended period. The present invention demonstrates the utility of cyclodextrin liposomes as a slow-releasing drug delivery system for biologically active substances, such as methotrexate. The present invention demonstrates the utility of less frequent intra-CSF administration for the prophylaxis and treatment of leptomeningeal leukemia or carcinomatosis in humans.

Detailed Description Text (81):
The in vivo studies were done on male BDF1 mice weighing 18-25 g. The group of mice was injected ip with 10 mg/kg of methotrexate in 1 ml of 0.9% NaCl as unencapsulated methotrexate control, cyclodextrin-methotrexate control (methotrexate 20 mg/ml; 2-hydroxypropyl1 -.beta.-cyclodextrin, 2 mg/ml; glucose, 6.4 mg/ml; free-base lysine, 8 mM; and HCl, 2 mM) or MVL-CD-MTX. Three mice were sacrificed and blood samples were collected from the jugular vein and placed in a heparinized tube at 0 hour (immediately after the injection), 1 hour and 4 hours after injection of the unencapsulated methotrexate or cyclodextrin-methotrexate complex; and 1, 5, 10 and 20 days after injection of MVL-CD-MTX. The plasma was separated and was kept frozen at -20.degree. C. until analyzed by the Emit.sup.R methotrexate assay on COBAS Fara Instrument. The Emit.sup.R assay is a homogeneous enzyme immunoassay technique based on the competition between drug present in the sample and drug labeled with the enzyme glucose-6-phosphate dehydrogenase for antibody binding sites. The limit of sensitivity was 0.02 .mu.M.

Detailed Description Paragraph Table (3):
TABLE 3 _____ Pharmacokinetic parameters of methotrexate after intraperitoneal administration Un- encapsulated MVL-CD-MTX MTX CD-MTX Free Total _____ PERITONEAL Conc. t.sub.1/2.sup.b (h) 0.54 0.46 39.6 45.6 Amount t.sub.1/2 (h) 0.45 0.41 .sup. NA.sup.d 62.4 C.sub.max.sup.c + SD 430 .+-. 13 379 .+-. 10 66.7 .+-. 18.3 1863 .+-. 168 (.mu.M) AUC (.mu.M .multidot. h) 233 316 12260 273800 PLASMA Conc. t.sub.1/2 (h) 0.9 0.6 240 NA Cmax.sup.c + SD 3.3 .+-. 0.03 3.3 .+-. 0.03 0.05 .+-. 0.05 NA (.mu.M) AUC (.mu.M .multidot. h) 11.2 12.2 18.4 NA _____ .sup.a cyclodextrin-methotrexate .sup.b halflife .sup.c peak concentrations .sup.d not applicable

CLAIMS:

1. A liposome comprising

water,

a biologically active, eater soluble compound encapsulated within the liposome, and

a cyclodextrin in a concentration of from about 10 mg/ml to about 400 mg/ml complexed with the compound within the liposome,

wherein the biologically active compound is released from the liopsome into an aqueous solution at about 37.degree. C. at a slower rate than from a cyclodextrin-free liopsome, and without substantial compromise to the therapeutic index of the biologically active compound.

3. The liposome of claim 1, wherein the water solubility of the biologically active

compound is greater that 1 .mu.g/ml in the absence of the cyclodextrin.

13. The liposome of claim 1, wherein said cyclodextrin is selected form the group consisting of .alpha.-cyclodextrin, .beta.-cyclodextrin, .gamma.-cyclodextrins, methyl cyclodextrin, ethyl cyclodextrin, hydroxyethyl cyclodextrin, hydroxypropyl cyclodextrin, branched cyclodextrin, cyclodextrin polymers, and monosuccinyl dimethyl .beta.-cyclodextrin.

14. The liposome of claim 12, wherein said cyclodextrin is 2-hydroxypropyl-.beta.-cyclodextrin.

18. A method of increasing the half-life of a water soluble biologically active compound in an animal in need thereof comprising administering to the animal a liposome encapsulating the compound, wherein said liposome further encapsulates water, and a cyclodextrin in a concentration from about 10 mg/ml to about 400 mg/ml complexed with said compound; whereby the half-life of the compound is substantially increased.

20. The method of claim 18, wherein water solubility of the biologically active compound is greater than 1 .mu.g/ml in the absence of the cyclodextrin, and the cyclodextrin forms an inclusion complex with the water soluble compound.

21. The method of claim 18, wherein said cyclodextrin is selected from the group consisting of .alpha.-cyclodextrin, .beta.-cyclodextrin, .gamma.-cyclodextrins, methyl cyclodextrin, ethyl cyclodextrin, hydroxyethyl cyclodextrin, hydroxypropyl cyclodextrin, branched cyclodextrin, cyclodextrin polymers and monosuccinyl dimethyl .beta.-cyclodextrin.

22. The method of claim 21, wherein said cyclodextrin is 2-hydroxypropyl-.beta.-cyclodextrin.

31. The method of claim 18, wherein the cyclodextrin is selected from the group consisting of .alpha.-cyclodextrin, .beta.-cyclodextrin, .gamma.-cyclodextrins, methyl cyclodextrin, ethyl cyclodextrin, hydroxyethyl cyclodextrin, hydroxypropyl cyclodextrin, branched cyclodextrin, cyclodextrin polymers and monosuccinyl dimethyl .beta.-cyclodextrin.

32. The method of claim 31, wherein the cyclodextrin is 2-hydroxypropyl-.beta.-cyclodextrin.

33. A method of treating a pathophysiological state in an individual in need thereof comprising administering a liposome to the individual, said liposome comprising a therapeutically effective amount of a water soluble, biologically active compound complexed with a cyclodextrin, wherein the concentration of the cyclodextrin is from about 10 mg/ml to about 400 mg/ml, and the biologically active substance and the cyclodextrin are encapsulated within the liposome; whereby the half-life of the compound in the individual is substantially increased.

34. The liposome of claim 3, wherein the compound forms an inclusion complex with the cyclodextrin.

35. The method of claim 20, wherein the compound forms an inclusion complex with the cyclodextrin.

38. The method of claim 33, wherein the water solubility of the compound is greater than 1 .mu.g/ml in the absence of the cyclodextrin, and the cyclodextrin forms an inclusion complex with the water soluble compound.

47. The method of claim 33, wherein said cyclodextrin is selected from the group consisting of .alpha.-cyclodextrin, .beta.-cyclodextrin, .gamma.-cyclodextrins,

methyl cyclodextrin, ethyl cyclodextrin, hydroxyethyl cyclodextrin, hydroxypropyl cyclodextrin, branched cyclodextrin, cyclodextrin polymers and monosuccinyl dimethyl .beta.-cyclodextrin.

48. The method of claim 47, wherein said cyclodextrin is 2-hydroxypropyl-.beta.-cyclodextrin.

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L2	$cyclodextrin adj5 oral$	204	L2
L1	$cyclodextrin and fentanyl and oral$	68	L1

END OF SEARCH HISTORY

L5: Entry 1 of 21 File: USPT May 25, 2004

US-PAT-NO: 6740639
DOCUMENT-IDENTIFIER: US 6740639 B1

TITLE: Inclusion complees of a high potent opioid peptide, pharmaceutical compositions and method of treatment

DATE-ISSUED: May 25, 2004

INVENTOR-INFORMATION:

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APPL-NO: 09/ 537088 [PALM]
DATE FILED: March 29, 2000

INT-CL: [07] A61 K 38/08, C07 K 7/06

US-CL-ISSUED: 514/17; 530/302, 530/330
US-CL-CURRENT: 514/17; 530/302, 530/330

FIELD-OF-SEARCH: 514/17, 530/302, 530/330

PRIOR-ART-DISCLOSED:

U.S. PATENT DOCUMENTS

Search Selected Search ALL Clear

	PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
☐	5855916	January 1999	Chiesi et al.	424/488

☐	5997856	December 1999	Hora et al.	424/85.2

FOREIGN PATENT DOCUMENTS

FOREIGN-PAT-NO	PUBN-DATE	COUNTRY	US-CL
463653	January 1992	EP	
2710268	March 1995	FR	

OTHER PUBLICATIONS

Nath et al. Novel Met-Enkephalin Analogue1 . . . Pharm. Res. vol. 31, No. 5, pp. 269-273, 1995.

ART-UNIT: 1654

PRIMARY-EXAMINER: Russel; Jeffrey E.

ATTY-AGENT-FIRM: Nath & Associates PLLC Novick; Harold L. Goldberg; Joshua B.

ABSTRACT:

The invention provides novel inclusion complexes of highly potent opioid peptide of L-Tyrosyl-D-alanyl-glycyl-N-methylphenylalanyl-glycyl-isopropylamide with cyclodextrin, pharmaceutical preparations containing these inclusion complexes of L-Tyrosyl-D-alanyl-glycyl-N-methylphenylalanyl-glycyl-isopropylamide with cyclodextrin derivatives, the complexes being better soluble in water and having improved biopharmaceutical properties such as lesser toxicity, better analgesic action and non-addiction properties.

11 Claims, 11 Drawing figures

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L5: Entry 9 of 21 File: USPT Feb 2, 1999

US-PAT-NO: 5866162
DOCUMENT-IDENTIFIER: US 5866162 A

TITLE: Pharmaceutical composition containing a drug/.beta.-cyclodextrin complex in combination with an acid-base couple

DATE-ISSUED: February 2, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Grattan; Timothy James	Guildford			GB2

US-CL-CURRENT: 424/466; 424/465, 424/489

CLAIMS:

I claim:

1. A pharmaceutical composition, for oral consumption in aqueous solution, comprising a propionic acid NSAID/.beta.-cyclodextrin clathrate, and a pharmaceutically acceptable acid-base couple, in a quantity sufficient to cause the propionic acid NSAID/.beta.-cyclodextrin clathrate to dissolve when the composition is mixed with cold water and provide a solution with acid or neutral pH, wherein the weight of the acid-base couple is greater than 1% of the weight of water in which the composition is to be dissolved, and wherein the ratio of .beta.-cyclodextrin to propionic acid NSAID is 0.8:1 to 10:1.

2. A pharmaceutical composition according to claim 1 wherein the drug is a lipophilic NSAID.

3. A pharmaceutical composition according to claim 2, wherein the drug is selected from the group consisting of ibuprofen, naproxen and ketoprofen.

4. A pharmaceutical composition according to claim 1, wherein the acid-base couple is an effervescent couple comprising a water soluble acidic substance, and a basic compound which, when combined, liberate carbon dioxide on neutralisation with acid.

5. A pharmaceutical composition according to claim 4, wherein the water soluble acidic substance is an edible organic acid.

6. A pharmaceutical composition according to claim 5, wherein the organic acid is selected from the group consisting of mono-basic, di-basic and tri-basic salts thereof.

7. A pharmaceutical composition according to claim 5, wherein the edible organic acid is selected from the group consisting of tartaric acid, citric acid and ascorbic acid.

8. A pharmaceutical composition according to claim 1, wherein the base is selected from the group consisting of alkali metal and alkaline earth metal carbonates, percarbonates and bicarbonates, and mixed carbonate salts.

9. A pharmaceutical composition according to claim 4 wherein the acid-base couple is an effervescent couple which comprises a water soluble acidic substance selected from the group consisting of citric and tartaric acid, and a base selected from the group consisting of sodium bicarbonate and carbonate.

10. A pharmaceutical composition according to claim 1 wherein the acid-base couple is a non effervescent couple comprising a water soluble acid and a conjugate base selected from the group consisting of sodium salt and potassium salt.

11. A pharmaceutical composition according to claim 10 which is administered as a solution in the pH range of about 4.0 to about 7.0.

12. A pharmaceutical composition according to claim 1, wherein the ratio of .beta.-cyclodextrin to drug is about 1:1 to about 5:1.

13. A pharmaceutical composition according to claim 1, in a form selected from the group consisting of a tablet, a powder and granules for reconstitution with water, and ready-to-drink preparations.

14. A process for the preparation of a pharmaceutical composition as claimed in claim 1, which process comprises the admixture of a drug/.beta.-cyclodextrin clathrate complex and an acid-base couple.

15. A method for oral dosing of a pharmaceutical composition according to claim 1, comprising administration of a therapeutically active dose of the drug as a complex with .beta.-cyclodextrin in aqueous solution.

16. A pharmaceutical composition, for oral consumption in aqueous solution, comprising a drug selected from the group consisting of ibuprofen, naproxen and ketoprofen, .beta.-cyclodextrin clathrate, and a pharmaceutically acceptable acid-base couple, in a quantity sufficient to cause the drug to dissolve when the composition is mixed with cold water and provide a solution with acid or neutral pH, wherein the weight of the acid-base couple is greater than 1% of the weight of water in which the composition is to be dissolved, and wherein the ratio of .beta.-cyclodextrin to drug is 0.8:1 to 10:1.

17. A pharmaceutical composition, for oral consumption in aqueous solution, comprising a drug selected from the group consisting of ibuprofen, naproxen and ketoprofen, .beta.-cyclodextrin clathrate, and a pharmaceutically acceptable acid-base couple, which comprises a water soluble acid and a conjugate base selected from the group consisting of sodium salt and potassium salt, in a quantity sufficient to cause the drug to dissolve when the composition is mixed with cold water and provide a solution with acid or neutral pH, wherein the weight of the acid-base couple is greater than 1% of the weight of water in which the composition is to be dissolved, and wherein the ratio of .beta.-cyclodextrin to drug is 0.8:1 to 10:1.

18. A pharmaceutical composition, for oral consumption in aqueous solution, comprising a drug selected from the group consisting of ibuprofen, naproxen and ketoprofen, .beta.-cyclodextrin clathrate, and a pharmaceutically acceptable acid-base couple, which acid component of the couple is edible

organic acids, and their mono-di and tri-basic salts, and the base component of the couple is selected from the group consisting of sodium carbonate, percarbonate, bicarbonates, and mixed carbonate salts, in a quantity sufficient to cause the drug to dissolve when the composition is mixed with cold water and provide a solution with acid or neutral pH, wherein the weight of the acid-base couple is greater than 1% of the weight of water in which the composition is to be dissolved, and wherein the ratio of .beta.-cyclodextrin to drug is 0.8:1 to 10:1.

19. A method for enhancing the solubility of propionic acid NSAID's in an aqueous solution which method comprises admixing an NSAID/.beta.-cyclodextrin clathrate wherein the ratio of .beta.-cyclodextrin to NSAID is 0.8:1 to 10:1; a pharmaceutically acceptable acid-base couple, wherein the weight of the acid-base couple is greater than 1% of the weight of cold water into which the composition is admixed, and which couple yields a solution with an acid or neutral pH.

20. The method according to claim 19 wherein the NSAID is ibuprofen, naproxen or ketoprofen.

21. The method according to claim 19 wherein the acid-base couple comprises a water soluble acid and a conjugate base selected from the group consisting of sodium salt and potassium salt.

22. The method according to claim 21 wherein the resulting pH of the cold aqueous solution is about 4.0 to about 7.0.

23. The method according to claim 19 wherein the molar ratio of .beta.-cyclodextrin to NSAID is 1:1 to 3:1.

24. The method according to claim 19 wherein the maximum level of the acid-base couple is 15% of the weight of the water into which it is added.

25. The method according to claim 19 wherein the acid component of the couple is edible organic acids, and their mono-di and tri-basic salts, and the base component of the couple is selected from the group consisting of sodium carbonate, percarbonate, bicarbonates, and mixed carbonate salts.

26. The composition according to claim 16 wherein the drug is ibuprofen.

27. The composition according to claim 16 wherein the drug is naproxen.

28. The composition according to claim 16 wherein the drug is ketoprofen.

29. The composition according to claim 17 wherein the drug is ibuprofen.

30. The composition according to claim 17 wherein the drug is naproxen.

31. The composition according to claim 17 wherein the drug is ketoprofen.

32. The composition according to claim 18 wherein the drug is ibuprofen.

33. The composition according to claim 18 wherein the drug is naproxen.

34. The composition according to claim 18 wherein the drug is ketoprofen.

35. The method according to claim 20 wherein the drug is ibuprofen.

36. The method according to claim 20 wherein the drug is naproxen.

37. The method according to claim 20 wherein the drug is ketoprofen.

38. The composition according to any of claims 1 to 10, 11, 12 or 13, wherein the drug is ibuprofen.

39. The composition according to any of claims 1 to 10, 11, 12 or 13, wherein the drug is naproxen.

40. The composition according to any of claims 1 to 10, 11, 12 or 13, wherein the drug is ketoprofen.

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L5: Entry 13 of 21 File: USPT Jan 28, 1997

US-PAT-NO: 5597583
DOCUMENT-IDENTIFIER: US 5597583 A

TITLE: Pharmaceutical composition

DATE-ISSUED: January 28, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Grattan; Timothy J.	Guildford			GB2

US-CL-CURRENT: 424/464; 424/400, 424/489, 514/937, 514/974

CLAIMS:

I claim:

1. A method for oral dosing of ibuprofen comprising administering to a patient an ibuprofen-.beta.-cyclodextrin complex in a solution comprising hot water, wherein the ibuprofen .beta.-cyclodextrin complex delivers a therapeutic dosage level of 100 to 600 mg ibuprofen in solution as a single dosage unit, in a pH range of 2.5 to 7.0, and wherein the .beta.-cyclodextrin of the ibuprofen-.beta.-cyclodextrin complex is derived from .beta.-cyclodextrin undecahydrate.

2. The method of claim 1 wherein the solution additionally comprises one or more of the group consisting of a preservative, a suspending agent, a flavouring agent, a bulking agent, a binder, an adhesive, a lubricant, a disintegrant, a colouring agent, a sweetening agent, an adsorbent, a thickener and a diluent.

3. The method of claim 1 wherein the solution additionally comprises one or more of the group consisting of an analgesic, an antiinflammatory, an antipyretic, an expectorant, an antihistamine, a decongestant and an antitussive.

4. A composition for oral consumption comprising an ibuprofen-.beta.-cyclodextrin complex in hot aqueous solution having a pH in the range 2.5 to 7.0, wherein said composition delivers a therapeutic dosage level of 100 to 600 mg ibuprofen in solution as a single dosage unit, and further wherein the .beta.-cyclodextrin of the ibuprofen-.beta.-cyclodextrin complex is derived from .beta.-cyclodextrin undecahydrate.

5. The composition of claim 4 further comprising one or more of the group consisting of a preservative, a suspending agent, a flavouring agent, a bulking agent, a binder, an adhesive, a lubricant, a disintegrant, a colouring agent, a sweetening agent, an adsorbent, a thickener and a diluent.

6. The composition of claim 4 further comprising one or more of the group consisting of an analgesic, an antiinflammatory, an antipyretic, an expectorant, an antihistamine, a decongestant and an antitussive.

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L5: Entry 14 of 21 File: USPT Jul 27, 1993

DOCUMENT-IDENTIFIER: US 5231089 A
TITLE: Method of improving oral bioavailability of carbamazepine

Brief Summary Text (4):
Carbamazepine, or 5H-dibenz[b,f]azepine-5-carboxamide, is a widely used anticonvulsant agent having the structural formula ##STR1## It is available in the U.S. as Tegretol.RTM. brand chewable tablets of 100 mg, tablets of 200 mg and suspension of 100 mg/5 mL, intended for oral administration as an anticonvulsant or as a specific analgesic for trigeminal neuralgia. Recommended maintenance dosage levels in adults and children over 12 years of age are 800-1200 mg daily, although up to 1600 mg daily have been used in adults. In children of 6 to 12 years of age, the maintenance dosage level is usually 400-800 mg daily.

Brief Summary Text (20):
Inclusion complexes of 2,6-di-0-methyl-.beta.-cyclodextrin with dibenzo[bd]pyran derivatives and salts having analgesic, antemetic and narcosis-potentiating activities have been described in Nogradi et al U.S. Pat. No. 4,599,327; increased water solubility and thus improved biological activity have been claimed for the complexes. A review of the pharmaceutical applications of such methylated cyclodextrins has been published by Uekama, Pharm. Int., Mar. 1985, 61-65; see also Pitha, Journal of Inclusion Phenomena 2, 477-485 (1984).

Brief Summary Text (23):
The improved, optimized preparation and purification of hydroxypropyl-.beta.-cyclodextrin has been described by Pitha et al, International Journal of Pharmaceutics, 29, 73-82 (1986). In the same publication, the authors have described increased water solubility for 32 drugs in concentrated (40 to 50%) aqueous solutions of hydroxypropyl-.beta.-cyclodextrin. The authors indicated this to be an extension of their earlier work with hydroxypropyl-.beta.-cyclodextrin, which was previously found effective for oral administration of the sex hormones to humans. Their later work reported in Pitha et al, International Journal of Pharmaceutics, 29, 73-82 (1986), has also been described in Pitha U.S. Pat. No. 4,727,064, dated Feb. 23, 1988. That patent claims a composition containing an amorphous complex of cyclodextrin and a drug, and a method of producing a stabilizing amorphous complex of a drug and a mixture of cyclodextrins comprising (1) dissolving an intrinsically amorphous mixture of cyclodextrin derivatives which are water soluble and capable of forming inclusion complexes with drugs in water; and (2) solubilizing lipophilic drugs into aqueous media to form a solution and form a solubilized drug/cyclodextrin complex. The patent describes the preparation of various substituted amorphous cyclodextrins, including hydroxypropyl-.beta.-cyclodextrin and hydroxypropyl-.gamma.-cyclodextrin, the latter by analogous condensation of propylene oxide and .gamma.-cyclodextrin.

Brief Summary Text (51):
In another aspect, the present invention provides use of a complex of carbamazepine with cyclodextrin selected from the group consisting of hydroxypropyl and hydroxyethyl derivatives of .beta.- and .gamma.-cyclodextrin, in the preparation of a medicament for oral administration to an animal in need of carbamazepine therapy.

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L5: Entry 19 of 21 File: USPT Jul 29, 1986

DOCUMENT-IDENTIFIER: US 4603123 A
TITLE: Compounds having antiinflammatory activity, obtained by complexation of piroxican with .beta.-cyclodextrin, and pharmaceutical compositions containing them

Abstract Text (2):
The compounds of the invention possess high antiinflammatory and analgesic activities, together with a considerably reduced gastrolesive action.

Brief Summary Text (2):
Piroxicam is a compound belonging to the class of the Non Steroidal AntiInflammatory drugs (NSAI) which, thanks to its remarkable analgesic and antiphlogistic activity, is effectively employed in the treatment of arthro-rheumatic diseases. On the other hand, piroxicam is responsible of lesive effects on the gastrointestinal mucosa, though at a lower extent with respect to other drugs of the same therapeutical class widely employed in the clinical praxis.

Detailed Description Text (51):
From the comparison of the plasma kinetics, it appears evident that, as far as the absorption is concerned, the two substances differ both from the qualitative and the quantitative standpoint; in fact, the plasma levels of the complexed form are extremely high (about 80% of the maximum values), and appear almost immediately (15 minutes after the administration); contemporaneously, the analysis of the AUCs in the time interval 0-2 hr makes evident a significant difference ($p<0.005$) in the two treatments. Also the differences of the plasma concentrations at almost all of the observation times and, consequently, the AUCs in the time interval 0-72 hr, are absolutely significant. In view of these results, it can be concluded that, in the dog, the formation of an inclusion complex between piroxicam and .beta.-cyclodextrin is capable of inducing not only an accelerated absorption, but also a global increase in bioavailability (about 40%). It must be pointed out that an immediate onset of therapeutically useful plasma levels is of primary importance for the analgesic action, which must be rapid and effective.

Detailed Description Text (52):
Kinetic of the analgesic activity

Detailed Description Text (53):
The kinetic of the oral analgesic activity of the complex piroxicam/.beta.-cyclodextrin in comparison with piroxicam was investigated by means of the phenylquinone induced writhing test, by evaluating the degree of protection displayed by the tested substances against a characteristic syndrome (writhing), induced upon intraperitoneal injection of 10 ml per kg of body weight of an aqueous solution of phenylquinone (0.02% in 5% aqueous ethanol). The employed experimental model is a slight modification of that described by Siegmund, J. Pharm. Exptl. Ther., 119, 184, 1957.

Detailed Description Text (56):
The obtained results again confirm the noteworthy increase of the absorption rate of piroxicam, when complexed by inclusion into the .beta.-cyclodextrin, in comparison with the active principle as such, following the oral administration. In fact, even 5 minutes after the administration, it was observed the 99% of the

maximum evidenced inhibition for the complex piroxicam/.beta.-cyclodextrin, whereas that observed for piroxicam as such at the same time was 78%.

CLAIMS:

4. A pharmaceutical composition useful as an analgesic, in unit dosage form comprising an effective amount of the inclusion complex of piroxicam and beta-cyclodextrin wherein said piroxicam and said cyclodextrin are in the ratio between 1:1 and 1:10 respectively and at least one pharmaceutically acceptable carrier.

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L5: Entry 20 of 21 File: DWPI Jan 19, 1999

DERWENT-ACC-NO: 1999-148474
DERWENT-WEEK: 199916

TITLE: Use of cyclodextrin(s) as a pharmaceutical carriers for oral administration - especially new cyclodextrin ester(s) of phenylacetic acid type antiinflammatory-analgesic compounds

Basic Abstract Text (1):
Esters of a phenylacetic acid type antiinflammatory and analgesic compounds with cyclodextrin are new. The active ingredients, phenylacetic acid series antiinflammatory and analgesic compounds (I), are absorbed at the large intestine after oral administration of the esters.

Standard Title Terms (1):
CYCLODEXTRIN PHARMACEUTICAL CARRY ORAL ADMINISTER NEW CYCLODEXTRIN ESTER PHENYLACETIC ACID TYPE ANTIINFLAMMATORY ANALGESIC COMPOUND

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L5: Entry 20 of 21 File: DWPI Jan 19, 1999

DERWENT-ACC-NO: 1999-148474
DERWENT-WEEK: 199916

TITLE: Use of cyclodextrin(s) as a pharmaceutical carriers for oral administration - especially new cyclodextrin ester(s) of phenylacetic acid type antiinflammatory-analgesic compounds

PATENT-ASSIGNEE: LEDERLE JAPAN LTD (LEDEN)

PRIORITY-DATA: 1997JP-0181855 (June 24, 1997)

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PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
JP 11012179 A	January 19, 1999		010	A61K031/72

APPLICATION-DATA:

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
JP 11012179A	June 24, 1997	1997JP-0181855	

INT-CL (IPC): A61 K 31/19; A61 K 31/405; A61 K 31/72; A61 K 45/00; A61 K 47/40

ABSTRACTED-PUB-NO: JP 11012179A
BASIC-ABSTRACT:

Esters of a phenylacetic acid type antiinflammatory and analgesic compounds with cyclodextrin are new. The active ingredients, phenylacetic acid series antiinflammatory and analgesic compounds (I), are absorbed at the large intestine after oral administration of the esters.

Also claimed is the use of cyclodextrin as a drug carrier capable of binding chemically to a physiologically active substance. After oral administration, the chemical binding substance is hydrolysed at the large intestine to release the physiologically active substance.

USE - The esters are particularly used for colon delivery technology.

ADVANTAGE - The esters exhibit reduced side effects such as gastrointestinal disorders.

ABSTRACTED-PUB-NO: JP 11012179A
EQUIVALENT-ABSTRACTS:

CHOSEN-DRAWING: Dwg.0/3

DERWENT-CLASS: B05
CPI-CODES: B04-C02B1; B10-C04C; B12-M10B; B14-C01; B14-C03;

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